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Distinguishing between Vascular Dementia and Alzheimer's Disease by Means of the WAIS: A Meta-analysis

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This study was intended to, meta-analytically, review whether the subtests of the Wechsler Adult Intelligence Scale are useful in differentiating between vascular dementia and Alzheimer's disease. We expected the Alzheimer's disease group to outperform the vascular dementia group on those subtests that require executive functions, whereas inferior performance of the Alzheimer's disease patients was expected on memory tests. Two steps in the analysis were undertaken in an attempt to clarify this issue. The first step consisted of including all studies examining Wechsler Adult Intelligence Scale subtest performance in vascular dementia and Alzheimer's disease patients. Secondly, a subcortical vascular dementia subgroup was distinguished and performance of this subgroup was compared to that of the Alzheimer's disease group.

Overall, the analyses showed that both the vascular dementia and, more strongly, the subcortical vascular dementia group revealed decreased executive functions on several subtests compared to the Alzheimer's disease group. The Alzheimer's disease group showed inferior performance on a single semantic memory test only compared to both the vascular dementia and the subcortical vascular dementia groups. These results indicate that several subtests of the Wechsler Adult Intelligence Scale can differentiate between these two clinical groups, and that most of these tests reveal more impaired performance in the vascular dementia group.

Introduction

Two of the most common observed variants of dementia are Alzheimer's disease (AD) and vascular dementia (VaD) (Desmond, 1996). Both subtypes of dementia present profiles with distinguishable cognitive deficits, like executive dysfunctioning in VaD compared to a pronounced memory deficit in AD (Freeman et al., 2000; Graham, Emery & Hodges, 2004; Looi & Sachdev, 1999; Traykov et al., 2002). Traykov and co-workers (2002) found that AD patients had inferior performance on free and delayed recall and recognition as opposed to VaD patients, while the VaD group made more perseverative errors on the modified card sorting test, a test of executive functioning (EF). In accordance, Freeman et al. (2000) observed a decrement in delayed recognition memory performance of a modification of the Rey-Osterrieth Complex Figure in AD patients compared to the VaD group,

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whereas the VaD group showed inferior performance on the copy condition, a condition strongly dependent upon working memory. However, differentiating these two clinical pictures based on neuropsychological tests remains indefinite (Almkvist, Fratiglioni, Aguero-Torres, Viitanen & Backman, 1999; Fahlander, Wahlin, Almkvist & Backman, 2002). Several reasons for this variability have been presented, including the heterogeneity in the diagnosis of VaD (Graham et al., 2004). Also, vascular risk factors, such as hypertension, that are known to cause brain damage and thereby cognitive impairment (Carmelli et al., 1999; Raz, Rodrigue & Acker, 2003) are present in both VaD and, to a lesser degree, in AD (Rockwood et al., 2000). Probably, the presence of these risk factors in both dementia subtypes contributes to an overlap in neuropathology and, hence, comparable cognitive deficits. In general, both subtypes of dementia are characterized by a different neuropathology. Micro-infarction, diffuse white matter disease and perivascular changes are the most prominent features of VaD, while amyloid plaques and neurofibrillary tangles normally typify AD (Kalaria, 2002). Accumulating evidence, however, indicates co-occurrence of these pathologies in VaD and AD (Kalaria, 2002; Kalaria & Ballard, 1999). For example, abnormalities in the white matter are present in both VaD (Giovannetti et al., 2001) and AD (Bigler et al., 2003; Tsiskaridze, Shakarishvili, Janelidze, Vashadze & Chikhladze, 1998). In line with these observations is that a cholinergic dysfunction, characteristic for AD, is also observed in VaD (Lojkowska et al., 2003). Furthermore, a 'mixed dementia' subtype, consisting of AD concurrent with cerebrovascular disease, is recognised (Rockwood et al., 2000). This might diminish the differentiation between VaD and AD based on cognitive task performance.

A neuropsychological profile occasionally applied to differentiate AD from other forms of dementia is the 'Fuld profile' (Fuld, 1984). This profile is based on the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955) and is composed of scores on the following subtests: Block Design, Digit Span, Digit Symbol Substitution, Information, Object Assembly, Similarities, and Vocabulary. Based on these subtests, a certain formula is composed which is indicative for the presence of AD. This formula is:

$$A > B > C \leq D, A > D,$$

in which A represents the average performance on the Information and Vocabulary subscale, B the average performance on the Similarities and Digit Span tests, C the average performance on the Digit Symbol Substitution and Block Design task, and D the performance on Object Assembly.

Originally described as a diagnostic marker of AD (Fuld, 1984), many studies failed to replicate this finding (Alexander, Prohovnik, Stern & Mayeaux, 1994; Gfeller & Rankin, 1991; Randolph, Mohr & Chase, 1993; Yamashita et al., 1997). Even though specificity is quite high (i.e., 88.5% demented patients of the non-Alzheimer type and 93.3% controls present with 'negative' Fuld profiles), sensitivity (i.e. successful identification of AD patients) is quite low (24.1%; Massman & Bigler, 1993). Perhaps not applicable as a composite score or profile and despite several studies revealing no differences between both clinical groups (Loewenstein et al., 1991; Loring, Meador, Mahurin & Lergen, 1986; Padovani et al., 1995; Starkstein et al., 1996), we hypothesize that several subtests of the WAIS could still serve to distinguish between AD and VaD. According to the idea of more prominent executive dysfunctioning in VaD compared to AD, *several* subtests might be more impaired in the VaD group than in the AD group, while performance on tests that require memory processes will be most affected in the AD group. Furthermore, by examining a subgroup of VaD patients, i.e. subcortical VaD (sVaD), we attempted to reduce the variability that exists in the diagnosis of VaD. Due to this increased homogeneity in study population as well as the strong involvement of the subcortical brain regions in

EF (Pohjasvaara, Mäntylä, Ylikoski, Kaste & Erkinjuntti, 2003), we hypothesize that the WAIS subtests will differentiate more profoundly between sVaD and AD.

Method

The topic of this review is to meta-analytically examine whether the subtests of the WAIS are useful to distinguish between VaD and AD groups. Despite the evidence of the strong resemblance in both neuropathology and pathophysiology between these two types of dementia, it is argued that VaD will be characterized by a more dysexecutive syndrome (Starkstein et al., 1996) while AD is accompanied by increased memory deficits (Rascovsky et al., 2002). We are fully aware that through the multi-factorial nature of the Wechsler subtests they require multiple cognitive functions and, hence, various brain areas for intact performance. Also, as mentioned previously, an overlap between both pathologies does exist, and both observations might diminish the possibility of distinguishing between VaD and AD based on cognitive performance. Nonetheless, a cerebral blood flow study showed that cerebral hypoperfusion is primarily present in the parietotemporal cortex in AD and more in the frontal areas in VaD (Nagata et al., 2000). There is ample evidence that the temporal lobe is strongly involved in memory processes whereas the frontal cortex plays a major role in EF (Chantal, Labelle, Bouchard, Braun & Boulanger, 2002; Culhane-Shelburne, Chapieski, Hiscock & Glaze 2002; Stuss, Floden, Alexander, Levine & Katz 2001). Therefore, we assume that executive dysfunctioning will characterize VaD patients whereas memory deficits will be most prominent in the AD group.

All subtests of the WAIS were examined separately. Whether a task requires primarily EF or mainly memory processes was based on existing literature. This literature consists of studies reporting factor analyses and correlations that reveal several WAIS subtests to be strongly related to tests of EF (e.g., Trail Making Test part B), and studies examining frontal versus either non-frontal or temporal lesions (or activity in these brain regions), as well as the effect of subcortical neuropathology (e.g., Parkinson's disease, Huntington's disease) on task performance.

In general, Digit Symbol Substitution and Digit Span are considered measures of EF (Royall et al., 2002). In addition, executive processes might be involved in reduced productivity in performing the Block Design, Picture Arrangement and Picture Completion tests (Lezak, 1995). Indeed, based on the literature, we expected more impairment in both the VaD and sVaD group for the following of these tests: Block Design (Johnson, Head, Kim, Starr & Cotman, 1999; Skranes et al., 1997; Wallesch, Curio, Galazsky, Jost & Synowitz, 2001), Digit Symbol Substitution (Boone, Pontón, Gorsuch, González & Miller, 1998; Mahurin, Velligan & Miller, 1998; Peavy et al., 2001), Picture Arrangement (Deckel, 1999; Hasselbalch et al., 1992; Peavy et al., 2001), and Picture Completion (Mahieux et al., 1998; Skranes et al., 1997). Also, the Object Assembly test does reveal frontal processing (Peavy et al., 2001; Randolph et al., 1993) and might involve an executive component. These tests, but not the other WAIS subtests, were also found to have the strongest loading on the same single factor (Ardila, Galeano & Rosselli, 1998) and do represent the Performance subscale of the WAIS, which supports that these tests measure overlapping cognitive abilities. With regard to the Digit Span test, studies do favour a key element of executive/frontal processes in the backward and much less or not in the forward version of this test (Hoshi et al., 2000; Leskelä et al., 1999). Therefore we expect more impairment in the VaD group on the backward version only. In contrast, the Information, Vocabulary, Comprehension and Similarities subtests have been described as tests of semantic memory (Kazui, Hashimoto, Hirono & Mori, 2003), and would be more impaired in the AD group. It is only for two out of these four tests that we expect a

stronger involvement of memory compared to EF processing, namely the Information and Vocabulary subtests (Dobbins & Russell, 1990). Results are unclear with regard to the Comprehension subtest (Butters, Goldstein, Allen & Shemansky, 1998; Peavy et al., 2001; Randolph et al., 1993). Since the Similarities subtest requires both memory functions and executive processing (Dobbins & Russell, 1990; Insingrini & Vazou, 1997; Slachevsky et al., 2004), it is not likely that the VaD and AD patients can be distinguished on this task. Also, the Arithmetic test might be more impaired in AD patients (Hirono et al., 1998), but arithmetic functions equally require frontal related processes (Dehaene, Molko, Cohen & Wilson, 2004; Rivera, Menon, White, Glaser & Reiss, 2002), such as working memory. This subtest together with the Similarities, Comprehension, and Digit Span forward tests probably do not differentiate between VaD and AD (Table 1).

An extensive search was performed in Pubmed and Web of Science using search terms such as 'Alzheimer's disease', 'vascular dementia' or 'multi-infarct dementia', 'WAIS', 'Wechsler' and all subtests of the WAIS. As many studies as possible were obtained examining performance and reporting the results separately of both demented groups on subtests of the WAIS. Several inclusion criteria were employed. To reduce the possible influence of the previously described heterogeneity in the diagnosis of both VaD and AD, only studies that administered standardized diagnostic criteria including imaging techniques such as Magnetic Resonance Imaging (MRI) were selected. These techniques increase the probability of accurate diagnoses and, presumably, reduce the possibility of including dementia patients with severe co-occurrence of both pathologies. Also, since both age and severity of dementia are strong predictors of cognitive performance, only those studies that examined a VaD and AD group that were comparable on these factors were included. Severity of dementia was frequently assessed with instruments such as the Mini-Mental State Examination (Folstein, Folstein & McHugh, 1975) and the Clinical Dementia Rating scale (CDR) (Berg, 1988). It is argued that the MMSE might be more sensitive to AD than VaD, due to its strong episodic memory load (Graham et al., 2004) and, hence, may not reflect the true level of impairment. However, since only a few studies extended the assessment of disease severity to several diagnostic instruments, no exclusion or inclusion criteria based on diagnostic tool could be accomplished. In case data concerning age and severity of dementia was available but no information on the compatibility of the groups on these measures was given, a t-test was performed to test for possible differences. The test used to indicate the global level of cognitive impairment had to be a deviant instrument from the Wechsler subtests we examined. For example, full WAIS IQ score was not viewed as an appropriate indicator of level of cognitive impairment, and neither were tests that examine only a single aspect of cognitive functioning (e.g., EF as assessed with the Trail Making Test). Inappropriate matching was also considered present in case no data about age or level of cognitive impairment in the clinical groups was provided. Finally, studies had to report data usable in this meta-analysis (means \pm SD). We additionally enrolled studies that compared performance of these two clinical populations on tasks from different batteries that are also part or resemble those of the WAIS, such as the Digit Span from the Wechsler Memory Scale (WMS) (Wechsler, 1945) or the Symbol Digit Modality Test (SDMT), a revision of the Digit Symbol Substitution test (DSS). The SDMT and DSS reveal high correlations (Bowler et al., 1990; Morgan & Wheelock, 1992) although the raw score of the SDMT tends to be lower than the one obtained on the DSS (Morgan & Wheelock, 1992). We do not expect this to affect our results because only relative scores (*d*-size) were entered into the meta-analysis. Since the subtests examined have sources of various origins, from now on they will be referred to as 'Wechsler subtests'.

Table 1
Hypothesized differences in task performance between AD and VaD patients

VaD < AD	AD < VaD	VaD = AD
Block Design	Information	Arithmetic
Digit Span backward	Vocabulary	Comprehension
Digit Symbol Substitution		Digit Span total
Object Assembly		Digit Span forward
Picture Arrangement		Similarities
Picture Completion		

The hypothesized neuropsychological profile to emerge when comparing the VaD and AD subgroups on all WAIS subtests. VaD < AD: AD patients outperform VaD patients; AD < VaD: VaD patients outperform AD patients; VaD = AD: performance is equal in both groups.

Meta-analysis

The meta-analysis was conducted using Comprehensive Meta-analysis, a statistical program developed by Borenstein and Rothstein (1999). Cohen's d , representing the effect size, was calculated for each study separately, which is done with the following formula: Cohen's $d = M_1 - M_2 / \sqrt{[(\sigma_1^2 + \sigma_2^2)/2]}$.

An overall d -value was computed with each effect size weighted for sample size of the study. Accordingly, effect sizes of .20, .50, and .80 were used as guidelines to define small, medium, and large effects, respectively (Cohen, 1988). When running a meta-analysis, two different types of effects—fixed and random—must be considered. Fixed effects are those in which studies are assumed to be comparable, that is, they are not heterogeneous. Random effects are adjusted to correct for heterogeneity and can be deduced from calculating the so-called Q-statistics (Hedges & Olkin, 1985). Since it is unlikely that the studies reviewed here included strictly comparable study samples, only random effects are reported.

The extensive literature search resulted in 33 studies examining Wechsler subtest performance in both AD and VaD groups. Inappropriate age and severity of dementia matching was present in 14 studies, which were therefore excluded from the meta-analysis (Almkvist, Backman, Basun & Wahlund, 1993; Chaves et al., 1999; Crawford, Parker & Besson, 1988; Gainotti, Parlato, Monteleone & Carlomagno, 1992; Gandolfo, Vecchia, Moretti, Brusa & Scotto, 1985; Gfeller & Rankin, 1991; Hagberg & Gustafson, 1985; Hier, Warach, Gorelick & Thomas, 1989; Inzelberg, Shapira & Korczyn, 1990; Mazzocchi et al., 1987; McCleary, Dick, Buckwalter, Henderson & Shankle, 1996; Neshige, Barrett & Shibasaki, 1988; Perez et al., 1975; Rabey, Neufeld, Treves, Sifris & Korczyn, 1996). Due to inadequate data reports, two more studies were excluded (Carlesimo, Fadda, Lorusso & Caltagirone, 1994; Fahlander et al., 2002). Finally, one study did not use any imaging technique to accomplish the diagnosis, which was therefore excluded from further analyses (Almkvist et al., 1999). Two studies did apply MRI to both groups and additional standardized diagnostic criteria (i.e., NINCDS-ADRDA) only to the AD group (Graham et al., 2004; Loewenstein et al., 1991), which we found sufficient for inclusion. This resulted in 16 studies to enter the meta-analysis (Table 2), which was conducted as follows. In the first analysis, all studies were enrolled. Secondly, to reduce the heterogeneity within the clinical group of VaD, studies examining subcortical vascular dementia (sVaD)

Table 2
Characteristics of the included studies

Authors	Number of patients	Age (SD)	SVaD	Diagnostic criteria applied ¹	Level of impairment ² (test)	Wechsler subtests examined	Results
Graham et al., 2004	AD: 19 VaD: 19	AD: 68.9 (8.6) VaD: 71.2 (7.8)	Yes	AD: NINCDS-ADRDA & MRI VaD: MRI	AD: 24.2 (3.7) VaD: 25.3 (3.8) (MMSE)	DSb, DSf (WMS-R)	AD = VaD
Yuspeh et al., 2002	AD: 47 VaD: 29	AD: 76.3 (5.2) VaD: 74.1 (8.2)	Yes	AD: NINCDS-ADRDA & MRI VaD: NINCDS-AIREN & MRI	AD: 24.2 (2.0) VaD: 25.2 (2.7) (MMSE)	SDMT	AD = VaD
Giovannetti et al., 2001	AD: 49 VaD: 42	AD: 77.2 (5.6) VaD: 79.4 (6.0)	?	AD: NINCDS-ADRDA & MRI/CT VaD: ADDTC & MRI/CT	AD: 21.3 (3.8) VaD: 21.1 (4.0) (MMSE)	S (WAIS-R)	AD = VaD ³
Matsuda et al., 1998	AD: 11 VDS: 5 VDW: 7	AD: 75.4 (5.3) VDS: 75.0 (7.6) VDW: 76.6 (4.9)	Yes	AD: DSM IV-R & NINCDS-ADRDA & MRI/CT VaD: DSM IV-R & HIS & MRI/CT	AD: 21.5 (3.6) VDS: 20.0 (3.5) VDW: 18.7 (3.2) (MMSE)	BD, DSS, OA, PA, PC (WAIS-R); DSb, DSf, (WMS-R)	AD = VDS = VDW (DSb, DSf, DSS, PA, PC) AD = VDW (BD, OA)
Mendez et al., 1997	AD: 30 VaD: 30	AD: 72.2 (6.7) VaD: 69.6 (6.5)	Yes	AD: NINCDS-ADRDA & HIS & clinical examination/ 'neuroimaging' VaD: HIS & MRI (VaD patients met the NINDS-AIREN criteria retrospectively)	AD: 19.2 (4.2) VaD: 21.1 (4.6) (MMSE)	DSS, I (WAIS-R)	VDS < AD (BD, OA) AD = VaD
Tei et al., 1997	AD: 22 VaD: 22	AD: 67.3 (9.1) VaD: 68.6 (7.3)	Yes	AD: NINCDS-ADRDA & DSM III-R & CT & HIS VaD: HIS & CT & DSM III-R	AD: 23.6 (1.4) VaD: 24.6 (2.0) (MMSE)	DSf, SDMT	AD = VaD

Continued

Table 2
Continued

Authors	Number of patients	Age (SD)	SVaD	Diagnostic criteria applied ¹	Level of impairment ² (test)	Wechsler subtests examined	Results
Yamashita et al., 1997	AD: 236 VaD: 29	AD: 73.5 (8.1) VaD: 75.9 (6.1)	?	AD: NINCDS-ADRD & MRI VaD: ADDTC & MRI	AD: 17.6 (4.6) VaD: 18.7 (4.6) (MMSE)	A, BD, C, DS, DSS, I, OA, PA, PC, S, V (WAIS-R)	Not specified
Starkstein et al., 1996	AD: 40 VaD: 20	AD: 72.3 (6.2) VaD: 72.5 (5.8)	Yes	AD: NINCDS-ADRD & CT/MRI VaD: ADDTC & CT/MRI	AD: 19.9 (6.3) VaD: 19.0 (7.1) (MMSE)	BD, S (WAIS); DSb, DSf (WMS)	AD = VaD
Erker et al., 1995	AD: 62 VaD: 20	AD: 73.2 (8.6) VaD: 74.5 (6.1)	?	AD: DSM III-R & CT VaD: DSM III-R & CT	AD: stages 5 and 6 VaD: stages 5 and 6 (GDS)	C, PA (WAIS-R)	AD = VaD
Padovani et al., 1995	AD: 16 VaD: 16	AD: 64.2 (7.4) VaD: 66.1 (6.1)	?	AD: NINCDS-ADRD & MRI & DSM III-R & HIS VaD: MRI & DSM III-R & HIS	AD: 22.9 (2.3) VaD: 23.5 (2.4) (MMSE)	BD, DSS, DSb, DSf, I, V (WAIS)	AD = VaD
Kertesz et al., 1994	AD: 103 VaD: 25	AD: 72.3 (8.1) VaD: 75.6 (7.6)	Yes	AD: NINCDS-ADRD & DSM III-R & modified HIS & MRI/CT VaD: DSM III-R & modified HIS & MRI/CT	AD: 103.5 (20.9) VaD: 97.1 (23.4) (MDRS, fulfilled by 79 AD and 20 VaD patients)	BD (WAB); OA, PA (WAIS-R)	VaD < AD
Villardita, 1993	AD: 48 VaD: 30	AD: 68.72 (6.62) VaD: 68.46 (6.26)	?	AD: NINCDS-ADRD & DSM III & MRI & HIS VaD: DSM III & MRI & HIS	AD: 16.87 (4.5) VaD: 16.89 (4.24) (BIMC)	BD (WAIS); DSb, DSf (WMS)	AD = VaD
Saletu et al., 1992	AD: 45 VaD: 51	AD: 82.84 (6.28) VaD: 80.88 (6.12)	?	AD: DSM III & Marshall-HIS & CT VaD: DSM III & Marshall-HIS & CT	AD: 16.1 (4.02) VaD: 17.3 (3.65) (MMSE) ⁴	DS, DSS (WAIS)	Not specified

Loewenstein et al., 1991	AD: 15 VaD: 15 ⁵	AD: 73.2 (7.0) VaD: 73.3 (6.5)	?	AD: NINCDS-ADRD & MRI VaD: MRI	AD: 22.93 (1.9) VaD: 23.53 (2.4) (MMSE)	BD, OA, S (WAIS-R)	AD = VaD
Saletu et al., 1991	AD: 54 VaD: 57	AD: ? VaD: ?	?	AD: DSM III & HIS & CT VaD: DSM III & HIS & CT	AD: 70 (6) VaD: 70 (8) (SCAG)	DS, DSS	Not specified
Loring et al., 1986	AD: 12 VaD: 12	AD: 69.1 (8.3) VaD: 69.7 (6.6)	?	AD: NINCDS-ADRD & modified HIS & CT VaD: modified HIS & CT	AD: 4.8 VaD: 4.3 (BDRS)	A, BD, C, DS, DSS, I, OA, PA, PC, S, V (WAIS)	AD < VaD (PC), AD = VaD (A, BD, C, DS, DSS, I, OA, PA, S, V)

A: Arithmetic; AD: Alzheimer's Disease; ADDTC: State of California Alzheimer's Disease Diagnostic and Treatment Centers; BD: Block Design; BDRS: Blessed Dementia Rating Scale; BIMC: Blessed Information-Memory-Concentration; C: Comprehension; CT: Computed Tomography; DS: Digit Span; DSb: Digit Span backward; DSf: Digit Span forward; DSM: Diagnostic and Statistical Manual of Mental Disorders; DSS: Digit Symbol Substitution; GDS: Global Deterioration Scale; HIS: Hachinski Ischemic Scale; I: Information; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental State Examination; MRI: Magnetic resonance Imaging; NINCDS-ADRD: National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NINCDS-AIREN: National Institute of Neurological and Communicative Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; OA: Object Assembly; PA: Picture Arrangement; PC: Picture Completion; S: Similarities; SCAG: Sandoz Clinical Assessment Geriatric Scale; SDMT: Symbol Digit Modality Test; V: Vocabulary; VaD: Vascular Dementia; VDS: Vascular Dementia with Subcortical lacunar infarcts; VDW: Vascular Dementia with extensive White matter lesions; WAB: Western Aphasia Battery; WAIS(-R): Wechsler Adult Intelligence Scale(-Revised); WMS(-R): Wechsler Memory Scale (-Revised).

AD < VaD: VaD patients outperformed AD patients; AD = VaD; performance was equal in both groups; VaD < AD: AD patients outperformed VaD patients.

¹We focused solely on NINCDS-ADRD, NINCDS-AIREN, ADDTC, DSM (for dementia screening) and HIS diagnostic criteria (including imaging techniques, which we mention separately but often are required to fulfil the diagnostic criteria, such as the NINCDS-ADRD) for these were the most frequent applied criteria in the studies examined here.

²If the MMSE was administered, we only report performance on that test to enhance direct comparison between studies. Occasionally, authors applied additional tests. Only when the MMSE was not administered in studies we report other tests of level of impairment.

³This is based on the raw score. A more detailed analysis in that study did show differences in performance between both patient groups. We do not mention that here, however, since we narrowed this review to the raw scores of the Similarities subtest.

⁴We calculated the scores.

⁵This is the number of mildly impaired patients examined in this study. Performance of the moderately impaired patients is not reported.

or VaD patients with subcortical damage as prominent pathology were selected. Erkunjintti et al. (2000) developed useful guidelines for sVaD: “small vessel disease as the primary vascular etiology, lacunar infarcts and ischemic white matter lesions as the primary types of brain lesions, and subcortical location as the primary location”. The selection for sVaD was accomplished as follows: first, studies examining multi-infarct dementia, characterized by multiple cortical and subcortical infarctions, which represents a subtype differing from sVaD (Romàn et al., 1993), were excluded. Even though multi-infarct dementia could be comprised of mainly subcortical infarcts with the cortical infarcts only representing a minority of the cases, the lack of detailed information about the occurrence of subcortical and, equally important, cortical lesions, supported the exclusion of those studies from the second part of the meta-analysis. Furthermore, we selected those studies that revealed primarily subcortical brain damage in their VaD sample. Taken together, seven studies were entered into this second analysis.

Results

In the presentation of the results, positive effect sizes indicate superior performance in the AD group while negative effect sizes suggest better performance in the VaD group.

Analysis 1: AD versus VaD

In the first analysis (Table 3), studies with groups matched on age and severity of dementia were included.

Table 3
Meta-analytic results when comparing task performance in the AD and VaD group

Wechsler Subtest	Analysis 1			Analysis 2		
	N total	<i>d</i> -value	P-value	N total	<i>d</i> -value	P-value
Arithmetic	289	−0.13	0.73	—	—	—
Block Design	603	0.06	0.78	174	0.69	0.003
Comprehension	371	−0.28	0.24	—	—	—
Digit Span	484	−0.03	0.86	—	—	—
Forward	275	0.07	0.58	165	0.19	0.23
Backward	231	0.31	0.02	121	0.47	0.01
Digit Symbol substitution	719	0.05	0.61	203	0.22	0.25
Information	381	−0.38	0.006	60	−0.49	0.07
Object Assembly	424	0.465	0.03	105	0.93	0.001
Picture Arrangement	479	0.21	0.37	108	0.78	0.001
Picture Completion	312	−0.06	0.91	23	1.02	0.02
Similarities	470	0.02	0.86	60	−0.06	0.83
Vocabulary	321	0.005	0.97	—	—	—

The obtained effect sizes when comparing performance of the VaD group with the AD group on all Wechsler subtests. In analysis 1 all studies were enrolled. Analysis 2 compared performance of the sVaD with the AD group. Positive effects indicate the AD group performed superior compared to the VaD group; negative effects suggest superior performance in the VaD group.

EF Tests. Two EF subtests revealed significant results, namely Object Assembly ($d = 0.465$; $p < 0.05$) and Digit Span backward ($d = 0.31$; $p < 0.05$). Using Cohen's guidelines, these results represent small effect sizes. The results indicate that the AD group outperformed the VaD group on both subtests. No further significant differences between the groups with regard to performance on EF tests were observed.

Memory Tests. The Information subscale reached statistical significance ($d = -0.38$; $p < 0.01$), although the effect size was small. Performance on the Information subscale was significantly better in the VaD group than in the AD group. No difference in Vocabulary task performance between the groups was observed.

Tests That Do Not Differentiate between AD and VaD. The tests for which there was no theoretical basis to expect inferior performance in either the AD or VaD group, such as the Similarities subtest, indeed did not reveal any group differences.

Analysis 2: AD versus sVaD

The second analysis (Table 3) included studies of sVaD patients. Four subtests (Arithmetic, Comprehension, Digit Span total, Vocabulary) have not been studied in the sVaD group and, hence, were not included in this part of the analysis.

EF Tests. Significant results were observed on the subtests Block Design ($d = 0.69$; $p < 0.01$), Digit Span backward ($d = 0.47$; $p < 0.05$), Object Assembly ($d = 0.93$; $p < 0.01$), Picture Arrangement ($d = 0.78$; $p < 0.01$), and Picture Completion ($d = 1.02$; $p < 0.05$). These effect sizes range from small (Digit Span backward) to medium (Block Design, Picture Arrangement) and large (Object Assembly, Picture Completion). All tests favoured AD patients as superior performers. The Digit Symbol Substitution test was the only EF test on which the AD and VaD group did not perform differently.

Memory Tests. The Information subtest, the only memory test examined here, was performed better in the VaD group and revealed a small effect size that was marginally significant ($d = -0.49$; $p = 0.07$).

Tests That Do Not Differentiate between AD and VaD. Again, the tests that were not expected to show any group difference indeed revealed no significant results.

Discussion

The present meta-analysis showed that the (s)VaD group performed worse on various subtests compared to the AD group. Conforming to the expectation, executive dysfunctioning seems more pronounced in sVaD compared to AD as indicated by several EF subtests (e.g., Digit Span backward, Object Assembly, Picture Arrangement). Memory dysfunction characteristic for AD compared to VaD patients was only indicated by decreased performance on the Information subtest, a test of semantic memory. The other semantic memory test, Vocabulary, was not examined in the sVaD group, which prevented comparing performance of the AD and sVaD group on this measure in this meta-analysis. The finding that most tests were not specifically affected in the AD group as compared to the (s)VaD patients, probably explains why the Fuld profile lacks sensitivity in diagnosing AD: the subtests do not measure those abilities in which AD patients normally show

decreased performance (Graham et al., 2004). Indeed, performance on memory tasks is hardly assessed by the Wechsler subtests that make up the WAIS. Especially episodic memory functions, as assessed with, for example, story recall, reveal more impairment in AD compared to VaD (Graham et al., 2004; Kertesz & Clydesdale, 1994; Padovani et al., 1995; Villardita, 1993), are not encountered with these Wechsler subtests.

Although executive dysfunctioning has frequently been shown to be characteristic for VaD (e.g., Desmond, 2004), this review indicates that, in contrast to previous reports, the Wechsler subtests do reveal a difference in performance between VaD and AD.

The multi-factorial nature of the Wechsler subtests implies that they address various cognitive functions and, as a result, impairment in each single cognitive function could already result in decreased performance. Tests such as the Block Design and Object Assembly test are often referred to as measuring constructional abilities (Lezak, 1995; Looi & Sachdev, 1999). However, EF such as strategy (Johanson, Gustafson & Risberg, 1986) or working memory (Freeman et al., 2000) can play an important role in constructional functions. Furthermore, a speed of processing component is present in several tasks as well, which might partly depend on EF (Desmond, 2004; Grigsby, Kaye & Robbins, 1995). It can be argued that a decrement in effective initiation and monitoring of behavior, both components of EF, could result in reduced speed of information processing. These are only a few examples of how EF might be involved in these tasks, and more thorough research about the precise involvement of various EF is warranted.

The studies included all employed a detailed diagnostic examination of both VaD and AD patients, including an MRI or CT-scan, through which the possibility of heterogeneity was at least partly reduced. More specifically, various authors report only including AD patients without characteristics indicative of vascular etiology, such as extensive white matter abnormalities, clinical strokes or focal neurological signs (e.g. Giovannetti et al., 2001; Graham et al., 2004; Tei et al., 1997; Yuspeh, Vanderploeg, Crowell & Mullan, 2002). We do realize that, instead of 'pure cases' of VaD and AD, 'mixed dementia' profiles are frequently observed and that these results, as a consequence, are not always directly applicable in dementia cases encountered by the clinician. However, we believe that this meta-analysis might contribute to a differentiation between VaD and AD by means of Wechsler subtests, with the Object Assembly, Information and Digit Span backward subtests appearing most sensitive.

One of the most important questions concerns the extent to which these results can be generalized. The studies included examined subjects ranging between 64.2 (+/-7.4) and 82.84 (+/-6.28) years of age, which covers quite a large segment of the demented elderly. The MMSE scores from the demented elderly ranged between 16.1 (+/-4.02) and 25.3 (+/-3.8), which represents the mild and moderate dementia stages, with little attention dedicated to the severely demented group. Equally, the other instruments that were applied revealed mild and moderate dementia in the majority of the cases (e.g., stages 5 and 6 from the Global Deterioration Scale in the study of Erker, Searight & Peterson, 1995). Therefore, these results are probably best applicable in the mild and moderate demented patients, but not the severely demented. One advantage is that most subjects undergoing neuropsychological assessments will be the mild or moderate demented elderly. Especially for the mild demented patients, who often present with vague complaints and less clear-cut evidence on imaging (e.g., MRI), the application of the Wechsler subtests might come in use for diagnosis. As for the severely demented group, it could be argued that these patients are way beyond being able to finish any neuropsychological tests at all and, hence, would never be administered any sort of extensive cognitive examination, such as all or several WAIS subtests. With standard neuropsychological tests, all severe demented

patients perform very poorly or are unable to complete any test, often regardless of how severe the dementia is (e.g., the MMSE-score can range from 0 to 16). In order to assess cognitive performance in severely demented patients a suitable instrument might be the Severe Impairment Battery (Panisset, Roudier, Saxton & Boller, 1994). With this battery, different levels of cognitive impairment that are present within a group of severe demented patients can be revealed. Therefore, the Severe Impairment Battery might be an appropriate measure of cognitive functions in this group.

The utility of the WAIS as a diagnostic tool for *intellectual functioning* in AD patients has been previously investigated using factor analyses. One recent study that examined the factor structure of the WAIS-R in AD patients (Davis, Massman & Doody, 2003) revealed three factors: Verbal Comprehension (Comprehension, Information, Similarities, Vocabulary), Perceptual Organization (Block Design, Digit Symbol Substitution, Object Assembly, Picture Arrangement, Picture Completion) and Freedom from Distractibility (Arithmetic, Digit Span). This structure is similar to that observed in healthy older adults (Burton, Ryan, Paolo & Mittenberg, 1994), which implies that the WAIS, despite not being a useful indicator of AD, is applicable in various clinical populations as an assessment of general intelligence. Although, to our knowledge, no factor analysis has been performed in VaD patients thus far, this battery might be a useful indicator of intellectual functioning in this group as well.

One point that warrants caution is that, despite several significant results in this meta-analysis, the majority of studies failed to successfully distinguish between VaD and AD based on the Wechsler subtest performance (e.g. Padovani et al., 1995; Villardita, 1993; Yamashita et al., 1997). This might indicate that the observed group differences are small. For example, we did find a significant effect size examining the only study that administered the Picture Completion subtest in sVaD patients ($d = 1.02$, $p < 0.05$), which was in contrast to the conclusion made by the authors themselves (Matsuda, Saito & Sugishita, 1998). One reason for this discrepancy might be the small sample size examined in this study ($n = 11$ and $n = 12$ for AD and VaD patients respectively). When calculating the overall d -value the sample size is taken into account and may strongly influence the strength of the observed effect-sizes. However, a d -value based on a single study, as was the case for the Picture Completion subtest, is independent from sample size. This can be an amenable explanation why the Picture Completion subtest reached significance in our study.

When running a meta-analysis there is always the risk of a publication bias, which refers to the possibility of only those studies that report positive results (i.e., group differences between AD and VaD patients) are being published while studies that reveal no group differences remain unpublished. Since the majority of the included studies did not report any group differences on the Wechsler subtests, we estimate the possibility of a publication bias in our study to be minimal. However, the almost continuous absence of any differences between VaD and AD patients within the studies examined here also indicates that only small group differences are present. Therefore, if applying the Wechsler subtests from the WAIS, the assessment should be extended with additional EF tests as well as tests tapping memory functions. A suggestion for memory tests would be to apply subtests from the Wechsler Memory Scale (Wechsler, 1945).

Finally, although this meta-analysis does indicate differences in performance *between* VaD and AD groups, nothing can be said about the diagnostic utility of the WAIS as an indicator of VaD or AD solely. For clinical purposes, information is required about how the performance on EF and memory tests relates to each other within individual patients, that is, is the cognitive impairment in VaD patients more severe for EF than for memory?

This meta-analysis cannot provide information to clarify this issue: group differences need not necessarily mean that raw scores of EF and memory tests differ within a patient. Although future research should be undertaken to examine this, indications do exist that the differentiation between semantic memory and EF within VaD and AD patients is legitimate. The fluency test poses an example of this, with the category and letter fluency most commonly administered. Both tests are occasionally referred to as measuring EF, although letter fluency is acknowledged as the most pure form of EF whereas category fluency is often denoted as a test of semantic memory. Interestingly, a dissociation between letter and category fluency tests in VaD and AD patients exists, in that AD patients perform worse on category compared to letter fluency (Carew, Lamar, Cloud, Grossman & Libon, 1997; Henry, Crawford & Phillips, 2004; Monsch et al., 1997) whereas the opposite is found in VaD patients (Carew et al., 1997). Possibly, this dissociation might also be present with respect to the Wechsler subtests, but for now it remains speculative.

The present findings stress the importance of reducing variability within the VaD group. Furthermore, group differences in performance on several Wechsler subtests were revealed. The results must be considered with caution, however, since they are based on a small number of studies; future studies should be undertaken to verify these findings. Furthermore, when comparing performance of the sVaD and AD group, only a single semantic memory test was included in the analysis. This hinders making any conclusions about the nature of the memory deficit in AD patients opposed to VaD patients as assessed with the Wechsler subtests.

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